REMARKS/ARGUMENTS

Claims 35 and 40-49 are currently pending. Applicant has amended Claim 40 to correct claim dependencies.

Claim Rejections - 35 USC § 112

Enablement

Claims 35 and 40-49 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilledin the art to which it pertains to make and/or use the invention for the reasons as set forth at pp2 para 4 in the previous Office Action.

The Examiner accepts that the instantly claimed polypeptides are known as AL-2, EFL-6 and currently ephrin-B3 in the art. The Examiner cites Cheng et al., (2002) as teaching that knock-out mice show no vascular defects, but defects in the corpus collosum. The Examiner cites Yu et al., (2003) as teaching that ephrin-B3 receptors are expressed on peripheral T cells and monocytes/macrophages. According to the Office Action none of the above references teach that ephrin-B3 plays any role in vascularization (page 3 of the Office Action).

The Examiner accepts that Pasquale (1997) and Gale & Yancopoulos (1999) teach that ephrinB2 and EPH receptors are involved in vascularization, however, neither reference allegedly provides any support for ephrin-B3 to be involved in vascularization (page 3 of the Office Action).

The Office Action states that the skilled artisan is not reasonably instructed as to which, if any, rate determining steps of neovascularization, variants, homologues, analogues, orthologues, fragments etc. which are encompassed by polypeptides which share 95% or greater sequence homology to the amino acid sequences of SEQ ID NO:2 and 4 are involved in a degree which is considered effective. Also, no evidence is allegedly present that any one of the variants will have any effect on neovascularization (page 4 of Office Action).

Applicants submit that the claims currently pending are fully enabled, such that, based on the teaching of the specification, one skilled in the art could have practiced the invention at the time the invention was made, without undue experimentation.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. [1] [2]. Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[3] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[4] [5]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important"[6] [7]. "Limitations and examples in the specification do not generally limit what is covered by the claims" MPEP § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction

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[1] MPEP §2164.0120

[2] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)) *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998))

[3] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)

[4] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)

[5] MPEP §2164.06.

[6] MPEP §2164.08

[7] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971)

in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[8]

The Disclosure provides sufficient information to enable the claimed invention

Claim 35 is directed to a method for accelerating neovascularization of a wound, comprising applying to the wound an angiogenically effective amount of a pharmaceutical composition comprising an isolated polypeptide comprising the sequence of (a) the mature human AL-2 amino acid sequence shown in Figure 1A-1C (SEQ ID NO:2) or Figure 2A-2D (SEQID NO4); or (b) a soluble AL-2 derived from SEQ ID NO:2 or SEQ ID NO:4; or (c) a mammalian homolog or a conservative amino acid substitution variant of (a) having at least 95% sequence identity with SEQ ID NO:2 or SEQ ID NO:4. Such polypeptides can be readily made and used to promote neovascularization of a wound following the directions provided in the specification, without undue experimentation.

SEQ ID NO: 2 and SEQ ID NO: 4 represent long and short forms of a native protein originally designated AL-2 (Genentech) or EFL-6 (Regeneron), and known as a member of the ephrin ligand family, now designated ephrin-B3 (see the attached Table 1 including the current nomenclature of Eph receptors and their ligands along with their synonyms).

The B-class ligands of the ephrin family are transmembrane proteins, which can be tyrosine phosphorylated upon receptor ligation. The cytoplasmic regions of ephrin ligands are highly conserved, and the ephrin ligands are promiscuous in their interaction with the Eph receptors. Thus most ligands have been shown to bind to multiple Eph receptors. For example, ephrin-B3 has been shown to bind EphA4, EphB1, EphB2 and EphB3. For more details of the Eph family of receptors and their ligands see the review article by Pasquale (Curr. Opin. Cell Biol., 9(5):608-5 (1997)) previously provided. The role of ephrins, including the ephrin-B

[8] *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

ligands in vascular development is also recognized in the art. See, e.g. the previously provided review article by Gale and Yancopoulos, Genes & Development 13:1055-1066 (1999).

The present specification indicates that the polypeptides of SEQ ID NO:2 and SEQ ID NO:4 are useful in promoting or enhancing angiogenesis and neovascularization. The Examiner is directed to pages 48, line 25 - page 49, line 27. The specification provides methods of administering the polypeptides (See pages 49 - 51).

The specification of the present application provides ample teaching about methods for making amino acid variants of SEQ ID NO: 2 and SEQ ID NO: 4, and for identifying variants that are expected to work in the claimed methods. The specification at Figures 4 and 5 provides a comparison of the sequence of AL-2 to Lerk2 and identifies regions of conserved sequence. Furthermore, at the priority date other, related polypeptides, such as AL-1 (now known as ephrin-A5) were known in the art. The experience gained with those polypeptides could be used as a guidance when derivatizing AL-2.

In particular, at the priority date of the present application one of ordinary skill could have used the AL-2 nucleic acid provided by the present inventors to identify other mammalian homologues of the AL-2 sequences specifically disclosed in the present application, without undue experimentation.

It is also taught in the specification, and was known at the priority date, that conservative amino acid substitutions can be made within a native sequence without compromising the desired biological activity. Possible conservative amino acid substitutions are listed in Table 1 on page 15 of the specification. Secondly, the specification discusses the types of conservative substitutions which could be made (See pages 13 - 17). Therefore, for an ordinary artisan, who in molecular biology is expected to have a Ph.D. and several years research experience, it would not have been a particularly difficult task to prepare the variants covered by the pending claims, and used them in the claimed methods with a reasonable expectation of success.

In view of the high degree of sequence identity and the known involvement of ephrin-B ligands in angiogenesis, at the priority date of this application a skilled artisan would have reasonably expected that mammalian homologues of the human sequences and conservative substitution variants having at least 95% sequence identity would be more likely than not work in the claimed methods, i.e. could be successfully used for neovascularization of wounds.

The specification provides a description of the regions of the AL-2 molecule. The specification defines "soluble" AL-2 as comprising only the extracellular (receptor binding) domain. (page 7, lines 8-12) The description for Figures 1A-1C and Figures 2A-2D indicates that the extra-cellular domain sequence includes amino acids Gly27-Pro219. It is also taught in the specification and was well known in the art at the priority date of this application that soluble variants of naturally occurring polypeptides either retain the biological activity of the membrane-bound molecule or can be brought in a biologically active form, and thus can be used in the same treatment methods as the full-length molecule, either on their own or in the form of fusion molecules, such as immunoadhesins, or in other clustered forms. Thus, on pages 30 and 31 of the specification, it is explained that even if the soluble form itself does not show significant biological activity (like in the AL-1), inactive soluble ligands can become biologically active when clustered, or are used in the form of ligand-IgG chimeras.

The Examiner relies of the teachings of Cheng and Yu as teaching other functions for ephrin-B3. Applicants note that in Cheng et al., (2002), the gene deleted in the knock-out mice was the EPHB3 receptor and not the ephrin-B3 gene. Therefore, this reference does not disclose a different function for the ephrin-B3 gene. Furthermore, as discussed above, Applicants have identified one function for ephrinB3. The fact that Yu may have identified other functions is not pertinent.

Accordingly, Applicants submit that the claims pending in this application are fully enabled, and respectfully request the reconsideration and withdrawal of the present rejection.

Written Description

Claims 35 and 40-49 were additionally rejected as allegedly failing to comply with the written description prong of 35 U.S.C. 112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

According to the rejection, patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to

enable members of the public to understand and carry out the invention. That requirement has allegedly not been met in the instant specification with respect to ephrin-B3 and variants thereof which have vascularization activity "(as noted above ephrin-B3 is not shown or taught to have vascularization activity unlike ephrin-B2)". (Page 5 of the Office Action). Secondly, the claims allegedly contain only structural but not explicit function parameters for the claimed variants. From this, the Examiner concluded that the specification does not provide adequate written description of the genus.

Applicants submit that, when assessing the indicia of patentability, including the written description requirement, the disclosure of the application as a whole must be considered through the eyes of one of ordinary skill at the effective priority date of the application. While only two specific sequences are disclosed in the present application, as discussed above, there is extensive teaching for making and using the other variants covered by the claims as currently amended. (Please see the discussion under enablement)

The case law is clear that the written description requirement for a genus can be satisfied by a combination of structural and functional features. The current claims do exactly that by reciting certain structural characteristics (e.g. soluble variants, at least 95% sequence identity) coupled with the requirement of a functional feature (angiogenic activity). Accordingly, applicants have conveyed with reasonable clarity to those skilled in the art, as of the filing date sought, that they were in the possession of the invention as of that date, and the present rejection should be withdrawn.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39766-0046DV1**).

Respectfully submitted,

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